Signaling mechanisms involved in resolution of inflammation

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Abstract

Inflammation is a physiological process that allows for a pathogenic agent to be eradicated and for damaged tissue to be repaired. It is controlled and ended by negative feedback mechanisms that allow for body homeostasis to be reestablished; but if inflammation persists, it generates a deleterious process in autoimmune diseases or it can contribute to conditions such as obesity and cancer. Inflammation resolution involves the participation of physiological phenomena that include a decreased proliferation and maturation of immune cells, as well as an induction of active leukocyte apoptosis and phagocytosis, and inflammatory mediator’s secretion inhibition and clearance. In this sense, it is plausible to orient therapy towards taking advantage of the physiological effects of receptors specifically participating in the resolution of inflammation by means of specific antagonists, since conventional pro-inflammatory mediator inhibition-oriented therapeutics show disadvantages due to disturbances to other physiological processes. In this paper, some of the mechanisms associated with the control of inflammation, which are the subject of ongoing research, are reviewed; particularly the receptors participating in the transduction of signals and that are relevant due to their therapeutic potential. (Gac Med Mex. 2014;150:437-46)

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Introduction

Inflammation is a complex physiological process whose function is to fight external pathogenic agents and/or to remodel damaged tissues through the secretion of a number of inflammatory mediators and the recruitment of immune cells. The inflammatory process is characterized by fluid extravasation to the site where the damage is located, which produces edema (tumor), increased blood flow (flushing), increased local temperature (heat) and activation of afferent terminals (pain), as well as, occasionally, loss of local function.

According to its duration, inflammation can be classified as acute and chronic. Acute inflammation is crucial for tissue repair; it involves an increase in vascular caliber, increased permeability for plasma proteins, as well as an activation and migration of leukocytes to the injured site. When the harmful stimulus persists or there is no satisfactory resolution of inflammation, it turns into chronic inflammation. Although inflammation is important to induce tissue repair and pathogen eradication, the lack of inflammation resolution leads to a chronic process and turns into a deleterious condition for the host.

The resolution of inflammation involves the participation of several physiological phenomena that include a decreased proliferation and maturation of immune cells, an induction of active leukocytes apoptosis and phagocytosis, as well as an inhibition of inflammatory mediators’ secretion and their clearance. These processes are carefully regulated by signaling molecules...
and cell interactions aimed to stop tissue damage, eradicate the pathogenic agent, and allow for tissue regeneration (Fig. 1)\(^7\). The mechanisms participating in the resolution of inflammation are several; however, those best characterized are: local resolution by arachidonic acid (AA) derivatives, resolution by discharges of the autonomous nervous system (ANS), resolution by anti-inflammatory cytokines and resolution by activation of receptors with immunoreceptor tyrosine-based inhibition motif (ITIM) domains. In addition to the abovementioned mechanisms, it is important to consider resolution by apoptosis induction in active immune cells through death receptors, but the study of these requires a detailed analysis and, therefore, they are not described in this review.

Various studies indicate that inflammatory conditions, especially the chronic ones, are associated with the onset of chronic degenerative diseases. Thus, studying the inhibitory control pathways of pro-inflammatory mediators’ secretion facilitates the generation of better strategies for the treatment of inflammation-associated conditions such as asthma, obesity, rheumatoid arthritis and cancer, among others. For a better understanding, the mechanisms involved in the resolution of inflammation, according to the previously mentioned classification, divided by sections, are briefly described below.

**Local resolution by fatty acid-derived mediators**

Different derivatives of the AA, such as the eicosapentaenoic acid (EPA) and the docosahexaenoic acid (DHA), modulate the activity of immunologic cells and are able to turn on or off the cells through the activation of different receptors and biosynthetic metabolic pathways (Fig. 2)\(^8\).

**Prostaglandins D\(_2\) and J\(_2\)**

Prostaglandin D\(_2\) (PGD\(_2\)) has immunosuppressing effects through the DP\(_1\) receptor and, to a lesser extent, due to the participation of DP\(_2\); both receptors are coupled to a G-protein (G-protein-coupled receptors, [GPCR]), in particular G\(_{\beta\gamma}\) and G\(_{\alpha}\), respectively\(^9\). PGD\(_2\) synthase-deficient mice display an exacerbated, acute and persistent inflammatory response, which they fail to resolve; whereas animals with synthase overexpression have a mild inflammatory process\(^9\). Additionally, PGD\(_2\) undergoes a non-enzymatic dehydration and forms biologically active prostaglandins of the J\(_2\) series (PGJ\(_2\)): PGJ\(_{12\,-14}\), PGJ\(_2\) and 15-deoxy-\(\Delta\)12-14-PGJ\(_2\) (15d-PGJ\(_2\)), which are characterized by the presence of an \(\alpha\), \(\beta\)-unsaturated ketone. Initially, the PGJ\(_2\) series was identified as the natural ligand of the peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\)). However, anti-inflammatory mechanisms are dependent and independent of PPAR-\(\gamma\), but they converge in the suppression of pro-inflammatory signaling pathways\(^8-10\).

**Lipoxins, resolvins and protectins**

Cyclooxygenase 2 (COX-2) produces the prostaglandin E\(_2\) (PGE\(_2\)), an eicosanoid that contributes to inflammation; however, an increase in the production of PGE\(_2\) has been shown to produce a negative feedback, which causes an inhibition of COX-2 and 5-lipoxygenase (5-LOX); furthermore, it induces the expression of 15- lipoxigenase (15-LOX), an enzyme in charge of the production of lipoxins (LX) in neutrophils\(^6\). LXs are a class of oxidized eicosanoids that bind to cell receptors and block the infiltration of neutrophils. Cell-cell interactions favor a transition in arachidonic products, from pro-inflammatory leukotrienes to anti-inflammatory LXs\(^11\). AA serves as a substrate of neutrophils’ 5-LOX to generate leukotriene A\(_4\) (LTA\(_4\)) and B\(_4\) (LTB\(_4\)), which have a proinflammatory function. However, tissue infiltration by neutrophils produces 15-LOX-expressing eosinophils, monocytes and epithelial cells with AA, LTA\(_4\) and LTB\(_4\), thus increasing the production of LX\(^11\). Bi-directionally, epithelial cells and other cells release 15S-hydroxyeicosatetraenoic acid (15S-HETE) and 15R-hydroxyeicosatetraenoic acid (15R-HETE), which are transformed into LX by neutrophils. Additionally, the leukocyte-derived LTA\(_4\) is recaptured by platelets and metabolized by 12-lipoxygenase (12-LOX) until LXA\(_4\) and B\(_4\) are produced\(^10\).

Acetylsalicylic acid (ASA) triggers the synthesis of 15-epi-lipoxin A\(_4\) (15-epi-LXA\(_4\)) as a result of acetylation of the COX active site in endothelial and epithelial cells. COX acetylation favors AA hydroxylation to form 15R-HETE by action of the cytochrome P450 (CYP450) and 5-LOX subsequent activity results in LXA\(_4\)\(^12\). Additionally, ASA-acetylated COX-2 reproduces the 15-LOX pathway, by modifying the acetylated enzyme activity in order to synthesize the 15R-hydroxyperoxyeicosatetraenoic from AA and, later, by the 5-LOX and epoxide hydrolase consecutive activity until 15-epi-LXA\(_4\) is synthesized, which is a unique property of this non-steroidal anti-inflammatory drug\(^13,14\). A similar mechanism is seen with statins.
(3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMG-CoA reductase] inhibitors) and pioglitazone (PPAR-γ-agonist), which induce the production of S-nitrosylated COX-2, which synthesizes 15R-HpETE, which finally is turned into 15-epi-LXA₄ by 5-LOX; it should be noted that both simultaneous post-translational modifications (S-nitrosylation and acetylation) inactivate this enzyme.¹³

The receptor identified for LXs is known as formyl peptide receptor-like (FPRL1), also named ALXR, and it is a receptor coupled to protein G that can also be activated by annexin 1 (ANXA1) and the serum amyloid A (SAA) protein; these ligands are potent inhibitors of cytokine migration, phagocytosis, and secretion from leukocytes processes in vitro and in vivo models, which results in an attenuation of the inflammatory process.¹⁵,¹⁶ LXs effects also include an induction of apoptotic neutrophils clearance by macrophages in vitro and in sites of inflammation in vivo.²⁰

In the last few years, other fatty-acids derivatives, also characterized by an anti-inflammatory activity, have been discovered, including resolvins, protectins and meresins.³,²¹ These lipidic markers are synthesized from fatty acids other than AA, i.e., DHA and EPA, known as omega-3 polyunsaturated fatty acids (ω-3 PUFA) or fish oils.³

D-series resolvins (D1, D2, D3, D4), protectin D1 and meresin 1 are DHA derivatives,¹⁴ and E-series resolvins are synthesized from EPA through an ASA-acetylated COX-2 activity-dependent pathway as an additional anti-inflammatory mechanism of the drug.¹⁴ Resolvin E₁ interacts with the LTB₄ receptor (BLT1) and with a partially agonist/antagonist effect on neutrophils.²²

During inflammation, the PGE₂- and PGD₂-activated signaling pathway initiates the transcription of the 15-LOX enzyme, which is required for the generation of LX, as well as of resolvins and protectins, as a “switch” to start the resolution of inflammation.²⁰ The identification of the endogenous lipidic ligands and their physiological effects through the formerly orphan GPCRs represents a huge advance in the search for new therapeutic targets, since the discovery or synthesis of

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Figure 1. Mediators participating in the resolution of inflammation. The inflammatory process is established by the participation of proinflammatory substances such as cytokines, prostaglandins, neuropeptides and physicochemical stimuli. These stimuli induce negative feedback mechanisms through the generation of soluble mediators and signaling proteins that allow for the inflammatory process to be regulated and resolved.
agonists that are specific to these receptors will allow for a new therapeutic armamentarium to be generated in the treatment of autoimmune diseases and other diseases associated with chronic inflammatory conditions (Fig. 2).

**Endocannabinoids**

Endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are involved with behavioral aspects, such as memory, learning, the reward system, addiction and anxiety. However, endogenous cannabinoids reduce the migration of dendritic cells through the CB$_2$ receptor, which causes the control of the inflammatory process$^{23}$; furthermore, they have been shown to inhibit interleukin (IL-2) production in activated T-cells, thus decreasing clonal expansion, which favors immunosuppression$^{24}$. The CB$_2$ receptor is abundantly expressed in the immune system cells and in a differential fashion as follows: B-lymphocytes $>$ natural killers (NK) $>$ neutrophils $>$ CD8+ T-lymphocytes $>$ CD4+ T-lymphocytes$^{25,26}$. Cannabinoids such

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Figure 2. Biosynthesis of anti-inflammatory lipid derivatives. Resolvins are synthesized from EPA and DHA, protectin and meresin are synthesized from DHA, whereas LXs and anti-inflammatory PGs are produced from AA. ASA has the particularity that induces the synthesis of specific molecules such as resolin E$_{1}$ and 15-epi-LXA$_{4}$. 

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as Δ9-THC suppress the release of proinflammatory cytokines, primarily the tumor necrosis factor-α (TNF-α), in B and T-cells37. Its anti-inflammatory effect is observed in several inflammatory pain animal models38. Δ9-THC can inhibit the initial immune response through the CB2 receptor, since it induces the release of anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF-β) in T-cells39. On the other hand, cannabinoids are well known for their psychoactive effects on the central nervous system (CNS) and, hence, we do not rule out for their effects on neural nuclei to provide a modulation on the immune system through circuits integrating afferent and autonomic efferent sensory information.

Resolution by ANS discharges

The nervous system modulates the immune response using different pathways, including the hypothalamic-pituitary-adrenal axis, as well as primary afferent and autonomous efferent terminals (cholinergic reflex by activation of α7 nicotinic receptors)30. The ANS is a link in the interaction of the immune system and the nervous system, and the sympathetic and parasympathetic efferences innervate lymphoid tissues such as the thymus gland, the bone marrow, the spleen, lymphatic nodes and gut-associated lymphoid tissues31.

Cholinergic reflex

(cholinergic anti-inflammatory pathway)

The release of acetylcholine (ACh) from parasympathetic ANS terminals inhibits the secretion of TNF-α and the synthesis of cytokines in visceral macrophages5. This is due to the existence of a vagal reflex that starts with an activation of afferent terminals of the vagus nerve by stimuli such as the gram-negative bacteria lipopolysaccharide (LPS) or by proinflammatory cytokines. In response to the stimulus, there is a vagus nerve motor reflex that suppresses the production of cytokines (Fig. 3). The main vagal efferent innervation involved with the cholinergic immunosuppressor reflex is on the spleen32.

The immune system cells express receptors for acetylcholine (AChR), which transduce an inhibitory intracellular signal; the best characterized cholinergic receptor in the process is the nicotinic receptor, which comprises the α7 subunit (α7 nAChR). Although the transductional mechanism involved with the cytokine-release control is not clear, the receptor-ligand interaction is known to cease with the decrease of nuclear factor κB (NF-κB) traslocation and to produce STAT3 activation via phosphorylation by JAK2, a kinase recruited by α7 nAChR that prevents the progression of inflammation (Fig. 3)33. Stimulation of the vagus nerve or administration of α7 nAChR antagonists inhibits the synthesis and release of TNF-α, IL-1β, IL-6, IL-8 and HMGB1; the effect can be reverted with a nicotinic receptor antagonist such as chlorisondamine34. However, nicotinic receptor subunit α7-knock out mice do not display TNF-α secretion suppression after vagus nerve stimulation and, during endotoxemia, the concentration of TNF-α, IL-1β and IL-6 is higher than in wild-type mice. This implies that the anti-sense oligonucleotide for α7 (which limits the available amount of this subunit), reverts the inhibitory effect of nicotine on LPS-induced TNF-α secretion in human macrophages, not so the oligonucleotides for α1 and α1035.

Sympathetic tone in inflammation

On the other hand, sympathetic ANS stimulation produces the release of noradrenalin on lymphoid organs, in addition to the stimulation of the hypothalamic-pituitary-adrenal axis37. The effect of chatecholamines on the immune system cells is controversial. In states of sepsis, activation of the α2-adrenergic receptor in the CNS reduces the sympathetic tone and the effect is associated with a reduced production and release of cytokines (IL-1β, IL-6 and TNF-α) by peripheral immune system cells38. Noradrenalin decreases bacterial phagocytosis by mature macrophages through an increase in cyclic adenosine monophosphate (cAMP) following the a and b-adrenergic receptors activation39. Furthermore, catecholamines induce lymphocyte apoptosis through the α1 and β1-adrenergic receptors with the activation of protein kinase C (PKC) and protein kinase A (PKA), respectively, which promotes a decrease in the inflammatory response40. Consequently, the cellular death processes that are independent of the activation of death receptors such as Fas Cell Surface Death Receptor (Fas) and TNF-related apoptosis-inducing ligand receptor (TRAIL-R) are a scarcely studied field; however, the understanding of
Figure 3. Inflammation modulation by the ANS. The ACh discharge by parasympathetic terminals stimulates α7 nicotinic receptors in immune cells that promote the inhibition of transcription factor NF-κB through STAT3 activation, similar to IL-10 receptor signaling. Sympathetic discharges on the adrenal cortex induce cortisol secretion, which activates intracellular glucocorticoid receptors that promote immunosuppression.

GPCR-induced death mechanisms will allow for controlled and more efficacious therapeutics to be generated and offered in chronic inflammatory conditions. Hypothalamic-pituitary-adrenal axis activation importantly contributes to the modulation of the immune response. Cortisol is a derivative of adrenal cortex-released cholesterol in response to stress and the sympathetic tone. Cortisol activates the glucocorticoid receptor (GR), which resides in the heat shock proteins (Hsp90 and 70)-bound cytosol. When cortisol binds to the receptor, it is translocated to the cellular nucleus to modulate gene transcription (Fig. 3)\textsuperscript{41}.

Resolution by anti-inflammatory cytokines

Interleukin 10 and TGF-β are the main anti-inflammatory cytokines participating in the resolution of inflammation. Both IL-10 and TGF-β are secreted by different cell lineages, such as regulatory T-cells (Treg)\textsuperscript{42,43} and myeloid-derived suppressor cells (MDSC)\textsuperscript{44}. The IL-10 receptor (IL-10R) belongs to the tyrosine kinase receptors with extrinsic activity through activation of the JAK2 enzyme and later phosphorylation of STAT3. These transductional mechanisms result in proliferation of the cell that contains the receptor and a marked reduction of immune response\textsuperscript{45}.

In turn, the TGF-β receptor has serine/threonine kinase activity and, in presence of the ligand, it produces an activation of Smads (formation of heterodimers between Smad 2 or 3 and Smad 4), which can modulate the gene expression of proinflammatory cytokines; in addition, it has been shown to be able to induce apoptosis in cells with TGF receptors and promote a decrease in the inflammatory process\textsuperscript{46}.

Resolution by activation of receptors with ITIM domains

Inflammation induced by immunoglobulin E (IgE)-antigen interaction on the membrane of mast cells promotes
anaphylactic reactions in patients and can be lethal; therefore, investigation focused on determining mechanisms able to inhibit IgE-antigen-induced degranulation in mast cells is relevant to the design of treatment strategies. The superfamily of better characterized inhibitory receptors comprises those containing a consensus sequence known as ITIM at the cytoplasmic region of the receptor (Table 1). ITIM is a motif comprised by six aminoacids (Ile/Val/Leu/Ser)-X-Tyr-X-X-(Leu-Val), where X represents any aminoacid. Tyrosine phosphorylation (by kinases of the Src family) recruits phosphatases with Src homology 2 (SH2) domains, for example, SH2-containing phosphatase 1 (SHP-1) and SHP-2, and the FcγRIIB receptor recruits SH2 domain-bearing inositol 5-phosphatases-1 (SHIP-1). The function of these phosphatases is to de-phosphorylate the immunoreceptor tyrosine-based activation motif (ITAM) tyrosines or to de-phosphorylate the phosphatidylinositol-3,4,5-triphosphate (PIP3). ITAMs contain two tyrosine residues, separated by 6-8 aminoacid residues and are located in the intracellular portion of proinflammatory mediators synthesis and release-inducing receptors, such as the high-affinity IgE receptor (FcεRI). Furthermore, receptors with ITIM domains

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Type-C lectin-inhibitory receptors

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Anti-inflammatory cytokine receptors

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<td>IL-10R</td>
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<td>JAK/STAT3</td>
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Nuclear receptors

| Glucocorticoids | GR | NF-κB inhibition and anti-inflammatory cytokines increase | Cortisol |
| Fatty acids | PPARγ | NF-κB inhibition and anti-inflammatory cytokines increase | PGJ2, AEA, PEA, PGI2 |
| | PPARα | NF-κB inhibition | PGI2 |

Protein G-coupled receptors and ionic channels

| Adrenergic | β2 | cAMP increase | Adrenalin/noradrenalin |
| Purinergic | A1a | cAMP increase | Adenosine |
| Prostanoids | DP1/DP2 | cAMP increase | EP2 |
| | FPRL1 | | |
| Cannabinoids | CB1 and CB2 | cAMP increase or decrease | Endocannabinoids |
| Cholinergic | α7 | Na+ channel, JAK/STAT3 | Ach, nicotine |

Table 1. Receptors involved in the resolution of inflammation that are present in immune cells

Adapted from50,55-57.
have been shown to inhibit the activity of receptors lacking ITAM sequences, such as proinflammatory cytokine-activated receptors and Toll-like receptors.

Multiple cell-surface receptors containing ITIM provide inhibitory signals to counteract immune cell activation. Inhibitory receptors are classified in two groups: those belonging to the superfamily of Ig receptors and type-C lectin-inhibitory receptors (Table 1). The superfamily of Ig receptors includes the family of CD300 receptors (CD300a and CD300f); in mice, the receptors gp49B1 (49-kd surface glycoprotein), the low-affinity IgG receptor or FcγRIIB (CD32B) and LAIR-1 were identified. These receptors suppress IgE-mediated mast cells degranulation in vivo and in vitro with the participation of SHP-1 and SHIP-1 in the inhibition of kinases Syk and Lyn. Co-ligation of FcγRII receptor with FcεRI receptor blocks the anaphylaxis reactions in the mouse through the activation of SHIP-1 phosphatase. The LAIR-1 receptor is able to bind to the c-Src tyrosine kinase (Csk), a kinase that negatively regulates the kinases of the Src family. The Hck and Fgr kinases also phosphorylate the PIR-B ITIMs by recruiting SHP-1 and SHP-2. Mast cells lacking the gp49B1 receptor degranulate excessively in response to antigen-IgE complexes. Some strategies can be implemented to prevent mast cells degranulation, including the design of antagonists to immunosuppressor receptors expressed in mast cells or molecules able to compete with the binding site between FcεRI and IgE.

On the other hand, there are also receptors lacking the ITIM motif that are able to inhibit the activation of mast cells by other not very well characterized mechanisms. Retinol, β2-adrenergic agonists and the CD63-binding extracellular matrix proteins are reported to be inhibitors of the function and proliferation of mast cells, as well as TGF-β has been shown to inhibit the Stem Cell Factor (SCF)-dependent growth of intestinal mast cells and IL-10. The ANS seems to modulate the activity of mast cells, since they express the nicotinic acid α4, α7 and β2 subunits. The β2-adrenergic receptors effectively inhibit antigen-dependent activation. PKA activation has opposed regulatory effects on the calcium release-activated calcium channel (CRAC) function.

There is cross-talk between the GPCR signaling and the signaling of inhibitory receptors with ITIM. Hck and Fgr kinases have a complex relationship with PIR-B; although the precise pathway is not known, Hck and Fgr kinases are known to phosphorylate the PIR-B receptor by recruiting SHP-1 and 2 for de-phosphorylation of unknown targets. The result is the suppression of immune cells activation (Fig. 4).
involved in the resolution of inflammation, including the proteins participating in the guanosine triphosphate hydrolyase (GTPase) activity of these receptors. For example, mast cells lacking the regulator G-protein signaling (RGS13) or RGS13\(^-\) protein show excessive IgE-induced anaphylactic responses and higher cytosolic Ca\(^{2+}\) concentration in response to several GPCR agonists, for example, adenosine, CXCL 12 and C5a. The RGS13 protein inhibits mast cells degranulation in an independent manner of the binding to G-proteins, through physical interaction with the PI\(_3\)K p85 regulator subunit, which prevents interaction with the Gab2 protein\(^{34}\).

Conclusions

Several studies indicate that inflammatory processes, especially those that are chronic, are associated with the onset of chronic degenerative diseases and, therefore, studying the negative control pathways of preformed mediators secretion in mast cells or other type of cells, such as MDSC, will help to generate better strategies for the treatment of conditions such as asthma, obesity and cancer. In this sense, it is plausible to orient therapeutics towards taking advantage of the physiological effects of receptors specifically involved with the resolution of inflammation using specific agonists, since proinflammatory mediator inhibition-oriented conventional therapeutics show disadvantages due to disturbances to other physiological processes.

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